

FXR MODULATORS

ABSTRACT OF THE DISCLOSURE

5 The present invention provides compounds, pharmaceutical compositions
and methods that are useful in modulating the farnesoid X receptor (FXR). As FXR is
involved in negatively controlling the expression level of cholesterol 7 α -hydroxylase
(*cyp7a*), the rate-limiting enzyme involved in the oxidative metabolism of cholesterol into
10 bile acids, the compounds described herein find utility in treating diseases associated with
abnormally high or low cholesterol levels. In certain aspects, the FXR modulators (*e.g.*,
antagonists) described herein block the negative feed-back downregulation of *cyp7a*
expression produced by certain cholic acids, the endogenous ligands for FXR. Moreover,
as FXR forms heterodimers with the retinoid X receptor (RXR) in some cell types,
modulation of the level of FXR activity in cells has a wide range of effects on a variety of
15 biological processes which are mediated by RXR or other RXR-interacting proteins such
as PPAR γ and PPAR α . Thus, compounds described herein are useful in treating other
biological activities such as obesity, diabetes, lipid associated disorders, cancer,
inflammatory disorders, disorders involving a disrupted or dysfunctional epidermal
barrier, and various other metabolic disorders.

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